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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
EWOLDT, GERALD R	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 05/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/347,064	ECK ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27,29,33-37,47 and 48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27,29,33-37,47 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 2/14/05 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendment, remarks, and 1.132 declaration of Dr. Martin Langer, filed 2/14/05, have been entered.

2. Claims 1-27, 29, 33-37, 47, and 48 are being acted upon.

3. In view of Applicant's amendment, all previous rejections under 35 U.S.C. 112, first paragraph, for lack of enablement have been withdrawn. In particular, the instant claims are drawn only to a nucleic acid encoding a fusion protein, a vector, a host cell, and a kit, none of which are inherently unpredictable. None of the claims currently recite a product intended only for *in vivo* use. Accordingly, the previous rejection based on the unpredictability of gene therapy and *in vivo* expression of DNAs has been withdrawn. Note that Remarks or sections of the Langer declaration relevant to the current rejections will be addressed as is appropriate.

4. The specification is objected to for the introduction of new matter into the specification. In the amendment, filed 2/14/05, Applicant added the terms "innate immunity" and "acquired immunity" to the specification. Applicant indicates that the declaration of Dr. Langer supports the addition. As set forth in paragraph 10 below, the amended material comprises the introduction of new matter into the specification.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-27, 29, 33-37, 47, and 48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

With regards to the instant claims, their breadth comprises a primary factor in establishing the unpredictability of the claimed fusion proteins. While Applicant argues in the instant Remarks that recitations of fragments and derivatives has been deleted from the claims (page 13), a review of the claims shows that this is simply untrue. Independent Claims 1 and 34 both recite a nucleic acid encoding at least a "fragment" of a protein and a nucleic acid having a sequence of at least a "fragment" of SEQ ID NO:1. Claims 2, 3, and 6 recite nucleic acids encoding at least one amino acid "deletion, substitution, insertion, addition or exchange" - most certainly these nucleic acids would comprise "derivatives". Also see Claims 8, 17, 18, 35, 36, 37, 47, and 48 for additional substitutions, exchanges and fragments. Note that none of the claims recite any limits on the number of substitutions, insertions, additions or exchanges, nor any minimum length on the fragment size. Thus, all nucleic acids could be substituted and fragments as short as single nucleotides could be encompassed by the claims. Applicant cannot credibly argue that the specification enables all of these embodiments.

Further regarding the nucleic acid fragments, substitutions, insertions, additions or exchanges of the instant claims, no functional examples of these nucleic acids are disclosed. The examples disclose only that bFGF-MLA and bFGF-MLA/rMLB comprise functional constructs (Examples 5 and 6).

While other constructs comprising only substitutions in the rMLB module (no deletions, insertions, additions or exchanges) are disclosed, they are not tested for functionality, thus, the disclosure of Example 7 is at best incomplete. Clearly then, the disclosure of the limited examples cannot by considered enabling for the entire breadth of the claimed invention.

Regarding the hybridization limitation of Claims 1, 5, 34 and 36, it is unclear what is intended to be encompassed by this limitation. Assuming that the nucleic acid is a double-stranded DNA, it appears that Applicant intends the invention to encompass a complimentary strand that is not the actual inverse of the coding strand and need not comprise the inverse of any DNA actually encoding a protein sequence. Numerous random changes to individual nucleotides in the hybridizing strand would likely render it nonsensical, while still capable of hybridizing, and sound scientific sense would indicate that said complimentary strand would not likely be of any coding use. It would seem then that the unpredictability of a complimentary nucleic acid strand that codes for nothing is inherently established.

In paragraph 17 of the Langer declaration, the Declarant indicates that effector fragments encompassed by the instant claims could be routinely tested for function by art known methods.

It appears that the Declarant is arguing that the skilled artisan might simply employ a method of trial and error to establish which fusion protein constructs might, or might not, be functional. It remains the Examiner's position that more is required, e.g., some guidance as to which fragments might be expected to comprise function and which might not. As set forth previously, a method of trial and error employing randomly selected constructs would provide no particular expectation of success with any particular construct, accordingly, the use of said method is considered to comprise undue experimentation.

In paragraphs 18-20 the Declarant argues that the skilled artisan would be well aware of art recognized processing, modulator, targeting, and affinity modules, or of how to assay for said modules.

While certain processing, modulator, targeting and affinity modules might well be known to the skilled artisan, said modules

comprising any and all possible substitutions, insertions, additions or exchanges, and fragment sizes would not be. And again, assay methods comprising no more than trial and error comprise undue experimentation as previously established.

7. Claims 1-27, 29, 33-37, 47, and 48 stand/are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed, for the reasons of record set forth in the paper mailed 10/22/01 and the reasons set forth below.

Under *Vas-Cath, Inc. v. Mahurkar* , 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession* of the invention, and that the invention, in that context, is whatever is now claimed.

There is insufficient written description to show that Applicant was in possession of the nucleic acid fragments, nor the nucleic acids comprising substitutions, insertions, additions or exchanges of the instant claims. Additionally, there is insufficient written description to show that Applicant was in possession of the effector, targeting, and modulator modules of the instant claims. Finally, there is insufficient written description to show that Applicant was in possession of the degenerate cell of the immune system of Claim 14.

Regarding the nucleic acid fragments, substitutions, insertions, additions or exchanges of the instant claims, as set forth above, no functional examples of these nucleic acids are disclosed. As no functional examples of these nucleic acids are disclosed, it is clear that a representative number of the essentially unlimited number of claimed nucleic acids have not been described.

Regarding the effector module of the instant claims, the specification at pages 11-12 discloses that the effector module encompasses not only modules that are toxic, but also modules that "modify the vital processes of the target cells", e.g., impaired "metabolic processes, particularly processes of the energy metabolism, molecular-genetic processes, particularly

translation, transcription and replication and specific cellular reaction sequences such as, e.g., the induction of apoptotic processes". Clearly, this term is intended to encompass a huge genus of effector modules, none of which, other than a single toxin (MLA), have been described. Thus, a representative number of the claimed nucleic acids have not been described.

Regarding the targeting module of the instant claims, the specification at page 13 discloses that the targeting module is "capable of allowing access of the fusion protein according to the invention to the cell's core via a specific affinity to a cell surface protein". Just a single example, of a cell surface protein meeting the required internalization limitation is disclosed (MHC). And indeed, only MHC Class II molecules actually meets the limitation allowing access to the cell's core (the more prevalent MHC Class I molecules would not be expected to be internalized). The claim at least implies, incorrectly, that any cell surface protein would allow access to a cell's core. Regardless, the single, only partially correct, example of a targeting module (MHC-binding peptides) does not comprise a representative number of the claimed nucleic acids.

Regarding the modulator module of the instant claims, the specification at page 17 discloses that the modulator module is capable of intracellularly modulating the cytotoxic effect of an effector module and include modules that assist in membrane translocation or those that participate in intracellular transport mechanisms. Just a single example, rMLB is disclosed. Again it is clear that this term is intended to encompass a huge genus of molecules, just one of which has been described. Thus, again, a representative number of the claimed nucleic acids have not been described.

Regarding the degenerate cell of the immune system of Claim 14, the claim at least implies that certain tumor cells comprise degenerate cells of the immune system, but does not indicate which. The specification provides no further edification. Thus, again, a representative number of the claimed nucleic acids have not been described.

At paragraph 29 of the declaration of Dr. Langer, the Declarant indicates that the skilled artisan would simply understand that a degenerate cell of the immune system refers to a tumor cell, and cites two references.

The Examiner was unable to find in either reference where tumor cells were referred to as degenerate cells of the immune system. Dr. Langer's assertion alone is insufficient to overcome the rejection.

8. Claim 14 stands rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the recitation of "a degenerate cell of the immune system" has not been defined in the specification and it does not appear to be an art recognized term as asserted by Applicant. Accordingly, the term renders the claim ambiguous and indefinite.

Applicant's arguments, filed 2/14/05 have been fully considered but they are not persuasive. Applicant argues that in the declaration of Dr. Langer it is asserted that the skilled artisan would simply understand that a degenerate cell of the immune system refers to a tumor cell, thus, the term is understood by those skilled in the art.

Applicant is advised that assertions alone cannot overcome the rejection. The submission of a published reference wherein "a degenerate cell of the immune system" is clearly defined might be more persuasive.

9. The following are new grounds for rejection.

10. Claims 10-13 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) the fusion protein of Claims 10 and 11 that "participates in acquired immunity,

B) the fusion protein of Claim 13 that "participates in innate immunity.

Applicant argues that support for the new limitations can be found in the declaration of Dr. Langer.

Applicant is advised that declaration of Dr. Langer has not been found to be convincing. At paragraphs 22-28 the Declarant argues that the terms specific and unspecific immunity were improperly translated. The Declarant indicates that support for his assertion can be found in PCT/EP98/00009 and Kuby (1997). A review of the references reveals no cites wherein innate immunity is referred to as unspecific immunity and acquired immunity is referred to as specific immunity.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

13. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

5/24/05

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Primary Examiner
Technology Center 1600